Chapter 5

Ovarian cancer in \textit{BRCA1/2} mutation carriers: The impact of mutation position and family history on the cancer risk

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ABSTRACT

Objectives: Assessing the combined impact of mutation position, regarding the ovarian cancer cluster region (OCCR), and type of cancer family history (FH) on age-related penetrance of ovarian cancer (OC) in women from BRCA1/2 families from the northern Netherlands.

Study design: A consecutive series of 1763 mutation carriers and their first-degree relatives from 355 proven BRCA1/2 families with a history of breast and/or ovarian cancer with in total 248 OC cases was included. Mutations were stratified for gene (BRCA1 or BRCA2) and location (within or outside the OCCR). FH was stratified for type of cancer occurring in first and second-degree relatives (OC only, breast cancer (BC) only or both OC and BC).

Main outcome measures: Cox-proportional hazard models were applied to estimate the OCCR effect, including and excluding a FH of cancer.

Results: Among BRCA1 families, OC risks were higher in women with OCCR mutations versus those with non-OCCR mutations (HR = 1.59, 95%CI = 1.19–2.12). This effect remained significant after adjustment for the type of FH (HR = 1.50, 95%CI = 1.11–2.01). In BRCA2 families, mutation position did not significantly affect the OC risk (HR = 1.50, 95%CI = 0.74–3.04). However, in the BRCA2 group, a FH including only OC presented by itself a strong impact on OC risk (HR = 4.63, 95%CI = 2.38–9.02), which remained stable after adjustment for mutation position (HR = 4.48, 95%CI = 2.28–8.81).

Conclusion: OCCR mutations significantly increased the OC risk in BRCA1 families regardless of the type of FH, but in BRCA2 families, type of FH seems to have a higher impact than mutation position on OC risk.
INTRODUCTION

At least 5–10% of ovarian cancer (OC) cases have a genetic predisposition, most often related to a BRCA1 or BRCA2 gene mutation. Where, the cumulative risk of developing OC until the age of 85 in the general population in the Netherlands is 1.5%, in women who carry a BRCA1/2 mutation the estimated risk to develop OC vary considerably, between 39% and 58.9% in BRCA1 and 11% and 34.5% in BRCA2.

Among BRCA2 mutation carriers, it has been observed that there is a higher proportion of OCs in comparison to breast cancers (BCs) when the mutation is located in the central part of the gene, coined as the “Ovarian Cancer Cluster Region” (OCCR). Later, a higher proportion of OCs to BCs was also observed in families with a mutation in the central part of BRCA1. The same studies reported higher OC lifetime risks for women with a mutation within the OCCR of BRCA1/2 genes. Additionally, there is evidence that BRCA2 families with OC are more likely to harbor mutations in the OCCR. Furthermore, studies have shown that regardless of the patients’ mutation status, a family history (FH) of OC is a strong risk predictor for developing OC, with relative risks varying from 1.1 to 24.0, depending on the number of affected relatives and their age at diagnosis.

The current study aimed at validating the current definition of OCCR in a large cohort of BRCA1/2 families from the northern part of The Netherlands by assessing the impact of the mutation position on the gene on the age-related penetrance of OC. Additionally, we aimed at assessing the combined impact of mutation position and type of FH on OC risk. More precise age-adjusted OC risk estimates would be of great importance on the counseling and decision making of BRCA1 and BRCA2 mutation carriers.

MATERIALS AND METHODS

- Setting

Patients in the northern part of The Netherlands in whom hereditary breast and/or ovarian cancer is suspected, are referred to the Clinical Genetics Department of the University Medical Center Groningen (UMCG). This is a genetically homogeneous population where several founder mutations have been detected. Mutation screening of the BRCA1/2 genes is offered if the patients or their families meet at least one of the following criteria: one BC case <35 years of age; two BC cases in first-degree relatives (FDRs) with one case <50 years of age; three or more FDRs with BC in two successive generations; one OC <50 years of age, two FDRs with OC, the occurrence of BC and OC in FDRs; the occurrence of a male BC. In each family, comprehensive BRCA1 and BRCA2 analysis is performed simultaneously, preferably in the patient with the highest prior probability of having a mutation. Once a family-specific mutation is identified, predictive testing is offered to all family members at
risk. BRCA mutation carriers and their FDRs are referred to a specialized multidisciplinary outpatient clinic in the UMCG for additional counseling on screening and preventive surgery.\textsuperscript{3,15,16}

- Women

From January 1997 to September 2011, information of 1044 female carriers who visited our specialized breast and ovarian cancer outpatient clinic and of 1309 female relatives of carriers was registered, yielding a database including data on 2353 women.\textsuperscript{3,17,18} For this study we selected mutation carriers (women with a proven BRCA mutation and obligate carriers, i.e., women with a child as well as a parent or sibling with the same mutation), and their untested female FDRs, who were at least 18 years old and of whom we had information on cancer incidence ($N = 1,889$). Women who did not have any first- or second-degree relative with BC or OC were excluded from this analysis ($N = 126$). A total of 1763 women were included, 1111 from BRCA1 families (588 mutation carriers and 523 untested FDRs) and 652 from BRCA2 families (359 mutation carriers and 293 untested FDRs).

Protection of the identity of the women included was guaranteed by assigning anonymous study-specific numbers, only known by two data managers. According to Dutch law, no further Institutional Review Board approval was needed for this study.

- Collected data

For all individuals, the following data were collected and analyzed: demographic characteristics, DNA testing results, personal history of cancer (with information on cancer site, age at diagnosis, treatment and follow-up), (age at) risk reducing surgery and FH regarding BC and OC including number of affected relatives and age of diagnosis. Follow-up data were retrieved from paper and electronic patient hospital files, which contain information obtained on recurrent visits to the UMCG family cancer clinic.

- Data definitions

The follow-up time for all women enrolled in the study was calculated from the date of birth until moment of censoring, which could be either age at diagnosis of OC, at risk reducing salpingo-oophorectomy (RRSO), at last moment of follow-up or at death.

Regarding mutation position, based on previous studies,\textsuperscript{6-8} BRCA1 and BRCA2 were each divided in 3 parts: upstream, OCCR and downstream. For this analysis, we classified the mutations into two categories: within the OCCR and outside of the OCCR. Mutations in the transition regions (present in 50 women in total) were considered as outside of the OCCR. FH was recorded as the number of affected first- and second-degree relatives with BC or OC. Two types of FH were discerned: ‘OC only’ and ‘BC with or without OC’.
- Statistical analysis

Characteristics of the women, their cancers, the mutation position regarding the OCCR and the FHs were described. The proportion of OC cases in relation to the total number of OCs and BCs in OCCR and in non-OCCR families was calculated. Logistic regression was applied to the subset of women with cancer to analyze the differences in the proportion of OC cases according to the mutation position in the gene, and odds-ratios (ORs) and 95% confidence intervals (95%CIs) were estimated.

Cox proportional hazard models were applied to test the impact of mutation position regarding the OCCR and of the type of cancer FH on age-related penetrance of OC. First, the impact of mutation position and type of cancer FH were assessed separately in a univariate model and hazard ratios (HROCCR_unadjusted and HRFH_unadjusted) and 95% confidence intervals (95%CIs) were estimated. Then a multivariate Cox proportional hazard analysis was applied. The impact of mutation position on the OC risk was estimated, where we corrected for the type of FH of cancer (HROCCR_adjusted). Subsequently, the impact of type of FH of cancer was estimated, where we corrected for the position of the mutation on the gene (HRFH_adjusted). The assumption of proportionality was checked by assessing the log-minus-log plots. Kaplan–Meier survival analyses were applied to visualize the combined impact of OCCR mutations and the type of cancer FH on cumulative incidence of OC by age.

To check for potential ascertainment bias, we repeated the analyses after exclusion of all women that had been diagnosed with BC or OC before the first *BRCA* mutation was detected in their family. To test for the impact of familial clustering on the estimates, a stratified Cox-regression model was applied, defining each family as one stratum. All tests were two-sided and P values below 0.05 were considered statistically significant. IBM SPSS version 20.0 was applied for the statistical analysis.

RESULTS

A total of 248 women were diagnosed with OC at a median age of 52.4 years (range: 22.6–88.3). The median age at OC diagnosis in the *BRCA1* group was 50.9 years (range: 22.6–87.5), which was significantly younger than in the *BRCA2* group (58.0 years, range: 29.9–88.3; Table 1).

We observed higher proportions of OCs over the total number of BCs and OCs among women with OCCR mutations, compared to women with non-OCCR mutations. This difference was statistically significant for *BRCA1* (OR = 1.76, 95%CI = 1.23–2.52), but not for *BRCA2* (OR = 1.96, 95%CI = 0.87–4.41; Table 2).

Among women from *BRCA1* families, an OCCR mutation was associated with an increased OC risk (HROCCR_unadjusted = 1.59, 95%CI = 1.19–2.12). In the *BRCA2* group, OCCR mutations did not significantly affect OC risks (HROCCR_unadjusted = 1.50, 95%CI = 0.74–3.04; Table 3). Concerning the type of FH, in the *BRCA1* group, a FH with only OC and no BC cases increased the risk of OC when compared to families with BC cases (HRFH_unadjusted = 1.68, 95%CI = 1.12–2.51). This risk increase was even more substantial in the
Table 1: Women, family and mutation characteristics.

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carriers* N (%)</td>
<td>588 (53%)</td>
<td>359 (55%)</td>
<td>947</td>
</tr>
<tr>
<td>Untested first degree relatives N (%)</td>
<td>523 (47%)</td>
<td>293 (45%)</td>
<td>816</td>
</tr>
<tr>
<td>Age at database update (2011), median (range)</td>
<td>52.7 (18–100)</td>
<td>54.8 (18–94)</td>
<td>53.4 (18–100)</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n among carriers</td>
<td>261 (69%)</td>
<td>154 (65%)</td>
<td>415</td>
</tr>
<tr>
<td>n among untested</td>
<td>115 (31%)</td>
<td>81 (35%)</td>
<td>196</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>42.8 (21.5–83.0)</td>
<td>46.6 (27.5–84.3)</td>
<td>44.5 (21.5–84.3)</td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n among carriers</td>
<td>122 (66%)</td>
<td>41 (66%)</td>
<td>163</td>
</tr>
<tr>
<td>n among untested</td>
<td>64 (34%)</td>
<td>21 (34%)</td>
<td>85</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>50.9 (22.6–87.5)</td>
<td>58.0 (29.9–88.3)</td>
<td>52.4 (22.6–88.3)</td>
</tr>
<tr>
<td><strong>OCCR position</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCCR mutation</td>
<td>411 (37%)</td>
<td>67 (10%)</td>
<td>478</td>
</tr>
<tr>
<td>Non-OCCR mutation</td>
<td>694 (63%)</td>
<td>585 (90%)</td>
<td>1279</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer only</td>
<td>113 (10%)</td>
<td>48 (7%)</td>
<td>161</td>
</tr>
<tr>
<td>Breast cancer only</td>
<td>442 (40%)</td>
<td>409 (63%)</td>
<td>851</td>
</tr>
<tr>
<td>Breast and ovarian cancer</td>
<td>556 (50%)</td>
<td>195 (30%)</td>
<td>751</td>
</tr>
</tbody>
</table>

Table 2: Number of cancer cases and the proportion of ovarian cancer over the total number of breast and ovarian cancers according to the mutation position in the gene.

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of cancer cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within OCCR</td>
<td>92</td>
<td>10</td>
<td>102</td>
</tr>
<tr>
<td>Without OCCR</td>
<td>94</td>
<td>52</td>
<td>146</td>
</tr>
<tr>
<td>BC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within OCCR</td>
<td>132</td>
<td>21</td>
<td>153</td>
</tr>
<tr>
<td>Without OCCR</td>
<td>238</td>
<td>214</td>
<td>452</td>
</tr>
<tr>
<td>Proportion of OC</td>
<td>0.41</td>
<td>0.32</td>
<td>0.40</td>
</tr>
<tr>
<td>OR (95%CI)</td>
<td>1.76 (1.23–2.52)</td>
<td>1.96 (0.87–4.41)</td>
<td>2.06 (1.51–2.82)</td>
</tr>
<tr>
<td>P value</td>
<td>0.002</td>
<td>0.099</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
BRCA2 group (HRFH_unadjusted = 4.63, 95%CI = 2.38–9.02). No differences on OC risk were observed when comparing women with only BC cases in their families to those with a FH including both OC and BC cases.

In the multivariate analysis, we observed that for the BRCA1 group the OCCR effect varied less than 10% after adjustment for a FH of cancer, remaining therefore stable (HROCCR_adjusted = 1.50, 95%CI = 1.11–2.01), but the effect of an OC only FH ceased to be significant after adjusting for mutation position (HRFH_adjusted = 1.49, 95%CI = 0.99–2.24). In BRCA2 families, the OCCR effect remained insignificant after adjustment for type of FH (HROCCR_adjusted = 1.25, 95%CI: 0.61–2.56). The effect of an OC only FH remained highly significant after adjustment for mutation position (HRFH_adjusted = 4.48, 95%CI = 2.28–8.81; Table 3). The combined effect of mutation position and type of cancer FH is presented in Fig. 1.

Table 3: Hazard ratios and 95% CIs for ovarian cancer according to mutation position in the gene and family history of cancer.

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>N of cases/women</th>
<th>Univariate models</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>P value</td>
</tr>
<tr>
<td>OCCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OCCR mutation</td>
<td>94/411</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>OCCR mutation</td>
<td>92/694</td>
<td>1.59</td>
<td>1.19–2.12</td>
</tr>
<tr>
<td>FH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC with or without OC</td>
<td>158/998</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>OC only</td>
<td>28/113</td>
<td>1.68</td>
<td>1.12–2.51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCA2</th>
<th>N of cases/women</th>
<th>Univariate models</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>P value</td>
</tr>
<tr>
<td>OCCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OCCR mutation</td>
<td>52/585</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>OCCR mutation</td>
<td>10/67</td>
<td>1.50</td>
<td>0.74–3.04</td>
</tr>
<tr>
<td>FH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC with or without OC</td>
<td>51/604</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>OC only</td>
<td>11/48</td>
<td>4.63</td>
<td>2.38–9.02</td>
</tr>
</tbody>
</table>

When excluding women diagnosed with cancer before the familial mutation was uncovered, 660 women were excluded: 424 from the BRCA1 group (270 mutation carriers and 154 FDRs) and 236 from the BRCA2 group (150 mutation carriers and 86 FDRs). The analyses in this subgroup revealed comparable figures. The OC risk was higher for OCCR mutations in women from BRCA1 families (HROCCR_unadjusted = 2.78, 95%CI = 1.28–6.03). In BRCA2 families, this OC risk seemed increased, but not statistically significant, most probably due to small numbers. Regarding the type of FH, a non-significant trend of risk increase was observed in BRCA1 OC only families. In the BRCA2 group there remained no cases of OC in the “OC only” FH group, therefore the impact of the type of FH of cancer could not be assessed (Table 4). In the multivariate model, the same trends were observed for BRCA1 families, but numbers were too small to reach significance. For BRCA2 no multivar-
iate model was possible because there were no OC cases left on the OC only FH group. The results from the analysis in which familial clustering was taken into account did not present any significant differences from the results obtained in the previous models.

**Table 4:** Bias corrected Hazard ratios and 95% CIs for ovarian cancer according to mutation position in the gene and family history (FH) of cancer by excluding patients who were diagnosed with cancer before a mutation was detected in the family.

<table>
<thead>
<tr>
<th></th>
<th>N of cases/women</th>
<th>Univariate models</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR 95%CI</td>
<td>P value</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OCCR mutation</td>
<td>11/433</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>OCCR mutation</td>
<td>18/255</td>
<td>2.78</td>
<td>1.28–6.03</td>
</tr>
<tr>
<td>FH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC with or without OC</td>
<td>24/629</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>OC only</td>
<td>5/61</td>
<td>2.33</td>
<td>0.89–6.15</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OCCR mutation</td>
<td>3/371</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>OCCR mutation</td>
<td>2/45</td>
<td>3.14</td>
<td>0.33–30.24</td>
</tr>
</tbody>
</table>

*No multivariate model was possible in the BRCA2 group because there were no cases of OC left in the “OC only” FH category.

**DISCUSSION**

In this single center hospital based study, including 1763 women with a BRCA1/2 mutation, we observed a higher proportion of OC cases relatively to the added BC and OC cases among families with OCCR mutations, comparing to families with non-OCCR mutations, both among BRCA1 (OR = 1.76) and BRCA2 women (OR = 1.96). In BRCA1 families, the OC risk was higher among women from families with an OCCR mutation versus those from families with a non-OCCR mutation (HROCCR_adjusted = 1.50). A non-significant trend of OC risk increase was observed for BRCA2 OCCR mutations (HROCCR_adjusted = 1.25), whereas, for these women, having an OC only FH was strongly correlated with a higher OC risk (HRFH_adjusted = 4.48).

The higher proportion of OC observed among women with BRCA1-OCCR mutations (OR = 1.76) was also reported in a study including women from BRCA1 families, where a higher proportion of OC relatively to BC cases was observed for women with mutations within the OCCR when compared to mutations in the 5′ (OR = 1.70) and 3′ regions (OR = 1.89). Among women from BRCA2 families, our study also found a higher proportion of OC relatively to BC in the OCCR mutation group (OR = 1.96). A stronger association between OCCR mutations and the OC/BC proportion has been described in a multicenter
Figure 1: Cumulative incidence of OC according to the mutation position on the gene and family history of cancer in BRCA1 (A) and BRCA2 (B) mutation carriers and their FDRs.
study (OR = 3.70 when compared to mutations 5′ and OR: 4.02 when compared to mutations 3′ to the OCCR).6

In women from BRCA1 OCCR mutation families we observed a higher OC risk (HROCCR_adjusted = 1.50). A multicenter study revealed a lower risk of OC for women with mutations 3′ to nucleotide 4191 (3′ boundary of the OCCR) when compared to women with mutations 5′ to it (RR=0.81).7 Among women from BRCA2 OCCR mutation families, our study revealed a trend of an increased OC risk (HROCCR_adjusted = 1.25), which has also been described in the literature. A higher risk of OC was observed for women with mutations within the OCCR when compared to women with mutations in the 5′ and 3′ parts of BRCA2 (RR = 1.88).6 However, when excluding a set of 25 families analyzed in a previous study,9 the OCCR effect ceased to be significant (RR = 0.85, 95%CI = 0.39–1.85).6 This variation was attributed to differences in ascertainment patterns between the two studies. Subsequently, another study found a non-significant trend of increase in OC risk among FDRs of BRCA2 OCCR mutation carriers when compared to FDRs of women with mutations 5′ or 3′ to the OCCR (RR = 3.6).20

We observed higher OC lifetime risks for women with an OCCR mutation in the BRCA1 cohort (HROCCR_adjusted=1.50, 95%CI=1.11–2.01) but not in the BRCA2 group (HROCCR_adjusted=1.25, 95%CI=0.61–2.56). The population in the northern Netherlands is genetically homogeneous with several founder BRCA1/2 mutations.21,22 In this population the penetrance of OC is high, with relatively high OC risk estimates for BRCA1/2 mutation carriers.3 In our BRCA2 population the most common mutations are outside of the OCCR, and only 10% of these women had a mutation within the OCCR.

Given the epidemiological evidence that the type of FH by itself affects OC risks,11-13 we tested the impact of type of FH on the OC risks in our population. An ‘OC only’ FH significantly increased the risk of OC when compared to families with BC in the BRCA1 group (HRFH_unadjusted = 1.68). However, this effect became less significant after adjusting for mutation position (HRFH_adjusted = 1.49), indicating that for these women the effect of FH is dependent on the OCCR position of the mutation. A FH effect on OC risks had been previously reported in a prospective study including BRCA1 mutation carriers, where a 1.6 fold increase on OC risk was observed for each relative with OC.14 In our BRCA2 population, having an ‘OC only’ FH had a strong effect on the lifetime OC risk (HRFH_unadjusted = 4.63). This effect remained comparable when adjusted for mutation position (HRFH_adjusted = 4.48), indicating that the effect of an ‘OC only’ FH is largely independent of the mutation position regarding the OCCR. There are no similar findings in BRCA2 cohorts reported in the literature.

The strength of our study is the large number of families, affected and unaffected family members, the periodic update of the data and the timespan of follow-up data. Another strength is the additional Cox-regression analyses performed excluding all cases diagnosed before first detection of the familial mutation, in order to check for possible ascertainment bias, and the stratified Cox-regression model for testing the impact of familial clustering on the presented estimates. These analyses show results comparable to those of the initial analyses, indicating that the presumed ascertainment bias and the effect of familial clustering are
likely to be small. A limitation of this study is the restricted number of categories in which both mutation spectrum (‘inside OCCR’ versus ‘outside OCCR’) and FH could be classified. We divided FH in 2 categories (‘OC only’ versus ‘BC with or without OC’) as the effect of a FH with both OC and BC cases on the OC risk was similar to the effect of a ‘BC only’ family. A study with a larger sample size might clarify this phenomenon.

In conclusion, this study shows that mutation position (OCCR or not) is the most significant predictor of OC risk in our BRCA1 population, whereas FH (‘OC only’ or not) has the highest impact in our BRCA2 population. Additionally, we observed that adding knowledge on the type of FH does not significantly change the OCCR effect on OC risks, indicating that OCCR and type of cancer FH have independent effects on OC risk in this population. Thus far no study considered the impact of mutation position adjusted for type of FH on OC risks. Information on both mutation position and FH is often available in the family cancer clinic setting, but are not yet combined for providing tailored care. Adequate estimation of age-specific risks is paramount because these are the cornerstones for decision-making on risk reducing options. This has become even more pressing since annual screening using ultrasound and CA125 was proven to be ineffective.23,24 This means that BRCA carriers face the dilemma of RRSO,25-29 which should be performed ‘in time’ to prevent OC, and not too early, to mitigate the adverse effects of early menopause. Currently, risk assessments used in counseling of BRCA mutation carriers are based on penetrance estimates, which show varying results worldwide.3-5 Additional studies in larger cohorts are needed to determine the real relevance of OCCR, specially for BRCA2, and whether other cluster regions are present that coincide with the type of cancer FH. We suggest that the results we present in this study, when confirmed in larger cohorts, could be used to refine risk estimates and further individualize counseling of BRCA1/2 mutation carriers for decision-making and timing on risk reducing options.

ACKNOWLEDGEMENT

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References


